UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' BRIEF IN SUPPORT OF *DAUBERT* MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT DANIEL CATENACCI, M.D.

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page No.

Cases

PRELIMINARY STATEMENT

Defense expert Daniel Catenacci, M.D., an oncologist, proffered the opinion that NDMA is not a known human carcinogen, in his report. However, during the course of his deposition, he conceded numerous points that undercut that opinion, including his concession that NDMA and NDEA are probable human carcinogens.

In addition, the methodology employed by Dr. Catenacci was marked with significant flaws that are fatal to his overall opinion on general causation. This begins with his admitted failure to consider the significant mechanistic evidence in the scientific literature demonstrating the similarity between the formation of DNA adducts and DNA damage in animal and human tissue due to NDMA exposure, which is the mechanism by which NDMA causes cancer in each. The failure to factor the mechanistic evidence into his analysis left out an entire category of significant scientific evidence.

This flaw was exacerbated by additional methodologic flaws, beginning with his admitted failure to evenly evaluate the valsartan human epidemiology studies he was relying on most heavily, Pottegård and Gomm. This was then layered with his ultimate concession that he needed more data to reliably incorporate Pottegård into his analysis after having rested a great deal of weight on that study in his report as the foundation for his ultimate opinion.

In addition, Dr. Catenacci relied on what he assumed to be substantial endogenous formation of NDMA to argue that the amount of NDMA in the valsartan would have been insignificant, yet he had no opinion as to how much is formed. Finally, he relied on two small studies showing lack of NDMA carcinogenicity in monkeys while unaware of, and not considering, compelling literature showing NDMA carcinogenicity in monkeys. These are not

"weight of the testimony" issues, these are methodological failings rendering the opinions speculative conclusions.

The foundation and conduct of Dr. Catenacci's analysis was unreliable. As a result, his opinions on general causation should be precluded.

STATEMENT OF FACTS

Daniel Catenacci, M.D. is an oncologist. He is not a toxicologist, epidemiologist, organic chemist, or risk assessor, nor is he holding himself out as an expert in these fields. (9/13/2021 Daniel Catenacci Dep. Tr. 76:14-16, 77:4-7, 77:8-78:1, Ex. A to the Certification of Adam M. Slater in Support of Plaintiffs' Motion).[1] He was "not reading up on the issues that are specific to [his] report" until he was contacted by Defendants, and has not published anything addressing the issues here. (*Id.* at 11:6-11, 46:7-47:11). He also confirmed that he performed a "qualitative assessment," meaning he performed no independent calculations, leaving such analysis to the epidemiologists and toxicologists. (*Id.* at 78:17-79:11).

Dr. Catenacci is not generally disputing the human carcinogenicity of NDMA and NDEA. Rather, in his report, he stated that he was asked to evaluate the opinion advanced by Plaintiffs' experts that "ingestion of NDMA at the trace levels detected in some valsartan drugs could have caused the cancers that the plaintiffs have alleged in this litigation." (Catenacci 8/27/21 Report, at 38, Ex. B). In his deposition, he defined the question he was answering as an evaluation of the cancer risk with "these levels in these pills." (9/13/2021 Daniel Catenacci Dep. Tr. 208:20-23). Accordingly, he is limiting his opinion to whether the actual dosages and NDMA/NDEA levels in

[1] Unless otherwise noted, all exhibits cited in this brief are attached to this supporting certification.

the contaminated valsartan could have caused the cancers claimed by the personal injury plaintiffs. (*Id.* at 210:21-211:19).[2]

A. Dr. Catenacci's Concessions.

During the course of his deposition, Dr. Catenacci conceded numerous points that undercut and notably contradicted the opinions set forth in his report. Among Dr. Catenacci's significant concessions:

- Dr. Catenacci agrees with IARC that NDMA and NDEA are probable human carcinogens. (9/13/2021 Daniel Catenacci Dep. Tr. 54:19-24, 115:10-12, 117:17-118:4).
- After he listed risk factors for cancer without including NDMA as a risk factor, Dr. Catenacci was confronted with an article he wrote with regard to biliary tract (liver) cancers, in which he stated in part that, "**known risk factors include . . . chemicals such as** . . . dioxin, **nitrosamines**, and asbestos . . ." (*Id.* at 155:5-158:11). He also confirmed that the association is based on "well-recognized papers." (*Id.* at 160:17-161:1)-.
- Dr. Catenacci agreed with statements in the Gomm human epidemiology study on health data for valsartan users in Germany, including: "NDMA is one of the most potent mutagenic carcinogens in animal models," and "**The immediate recall of all potentially NDMA-contaminated valsartan drug products by regulatory authorities worldwide was necessary in order to protect public health**." (*Id.* at 240:21-241:4; 9/14/2021 Daniel Catenacci Dep. Tr. 286:23-287:5, emphasis added, Ex. C).

[2] Dr. Catenacci was clear that he was not addressing the question of whether the risk was unacceptable such that the contaminated pills should not have been sold. (9/13/2021 Daniel Catenacci Dep. Tr. 119:17-120:2).

- Dr. Catenacci authored a book chapter with regard to risk factors for gastrointestinal cancers, and in the context of discussing that publication, he agreed that nitrosamines are associated with gastric cancers. (9/13/2021 Daniel Catenacci Dep. Tr. 49:4-21).
- There was no benefit whatsoever to the presence of NDMA in the contaminated valsartan pills. (*Id.* at 179:1-8).
- **He is not saying there was no carcinogenic risk to humans from ingesting NDMA in the contaminated valsartan pills**, rather he is quantifying the risk, with reference to the levels found in the contaminated pills. (*Id.* at 201:1-6).
- He agrees with the conclusion by Richard Adamson, the author of studies regarding monkeys which he relied on, with regard to NDMA contamination of valsartan and other medications. Specifically, "It is thus incumbent on industry and the FDA to take steps to identify and eliminate the sources of contamination of medications with this class of carcinogen." (9/14/2021 Daniel Catenacci Dep. Tr. 370:1-19 (quoting Adamson & Chabner, *The Finding of N-Nitrosodimethylamine in Common Medicines*, Oncologist. 2525:460-462, at 46 (2020), Ex. D)).
- He has no opinion as to whether a study could be approved in which the contaminated valsartan at issue here, with levels above the FDA's acceptable intake levels, would be given to test subjects and compared to a control group that did not take contaminated pills. (*Id.* at 317:16-319:22).
- Dr. Catenacci did not assess the FDA established acceptable intake levels in performing his analysis, and did not try to calculate an alternative acceptable daily intake. (9/13/2021 Daniel Catenacci Dep. Tr. 119:22-120:2; 9/14/2021 Daniel Catenacci Dep. Tr. 389:14-20).

- Dr. Catenacci disregarded and did not take into account the few corporate documents he was provided, and none influenced his opinions at all—including, for example, the toxicological risk assessments performed by and for the manufacturers. One of which stated in part, [redacted] (9/13/2021 Daniel Catenacci Dep. Tr. 111:13-115:8; 9/14/2021 Daniel Catenacci Dep. Tr. 375:8-377:3, 405:5-17, 424:9-426:8; TEVA-MDL2875-00056962, Ex. E).

B. Dr. Catenacci's Methodological Gaps.

1. The Failure to Consider the Mechanistic Data.

Dr. Catenacci's methodology appears to be the "weight of evidence" approach. He testified that his methodology involved consideration of human epidemiology studies, occupational studies, dietary studies, and animal studies. (9/13/2021 Daniel Catenacci Dep. Tr. 218:17-219:8). This left a significant gap since he did not address an entire category of relevant scientific evidence that was considered by Plaintiffs' experts, the mechanistic evidence.[3]

[3] For example, Plaintiffs' expert pathologist Stephen Lagana, M.D. stated in part in his report:

> NDMA causes cancer by various mechanisms. One is by acting as an alkylating agent. Alkylating agents are substances which attach an additional compound (an "alkyl" group, in this case) to DNA. NDMA is converted to methyldiazoniumion. This compound further degrades into something which interacts directly with replicating DNA and adds an alkyl group. This alkyl group can break the DNA apart and makes DNA replication more difficult and can lead to failures or errors (mutations) during replication. If one of these mutations causes a cell to become immortalized, then that can be the start of a cancer. As this mechanism of injury is mainly germane to dividing cells, the risk is likely greater in organs in which the cells replicate frequently (e.g. gastrointestinal tract). A second mechanism is the activation of RAS family oncogenes. Oncogenes are genes which cause cancer, mainly by driving cells to duplicate.

Dr. Catenacci ignored the mechanistic evidence in the scientific literature despite the fact that the list of materials considered that was attached to his report included an article addressing this subject. However, the article is not discussed or even cited in the actual report, and no opinions reference that or any article with regard to the import or even existence of the mechanistic studies. Dr. Catenacci confirmed that the failure to reference or discuss an article in the report meant that it was not of any importance to his analysis. (9/13/2021 Daniel Catenacci Dep. Tr. 128:5-14). The article, titled "Mechanisms of action of *N*-Nitroso compounds," states at the outset:

> There is ample evidence from studies in experimental animals that *N*-nitroso compounds are carcinogenic because in the body they form potent electrophilic alkylating agents. These reactive intermediates are formed by spontaneous decomposition in the case of nitrosoureas and related compounds, or by metabolic activation in the case of *N*-nitrosamines. The electrophiles subsequently react with DNA of target tissues to form altered bases which leads to the initiation of carcinogenesis. **There is now convincing evidence that the biological activity of *N*-nitroso compounds in humans does not differ substantially from that in experimental animals. We can therefore predict with a high degree of confidence that**

> RAS oncogenes are common drivers of cancer, particularly in the lung, pancreas, gastrointestinal tract, skin, thyroid, blood and uterus.
>
> * * *
>
> [T]he World Health Organization presented a summary analysis of the animal studies, and mechanisms whereby NDMA could cause cancer, as well as dietary literature. The authors observed that, "Putative pathways for the metabolism of NDMA are similar in rodents and humans, and indeed the formation of O6-methylguanine has been detected in human tissues exposed to NDMA." They concluded, "Therefore, owing to the considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumour formation, and the apparent lack of qualitative species-specific differences in the metabolism of this substance, **NDMA is highly likely to be carcinogenic to humans**."

(Lagana Report, at 5-6, 12-13, 22 (footnotes and citations omitted), Ex. F; *see also, i.e.*, Etminan Report, at 27, Ex. G; Panigraphy Report, at 45-76, 153-177, Ex. H).

> ***N*-nitroso compounds including nitrosamines are carcinogenic in man**.
>
> * * *
>
> It seems unlikely, therefore, that humans will be resistant to the carcinogenic action of these compounds.

Archer & Michael, *Mechanisms of action of N-nitroso compounds*, CANCER SURVEYS 8, 241, 247 (1989), Ex. I. That article cites to another study of human tissue, which was NOT cited to, mentioned, or discussed by Dr. Catenacci. (*Id.* at 246, 248). That article, discussing a study of human liver specimens after a fatal case of presumed NDMA poisoning, stated in part:

> The results indicate for the first time that humans, like rodents, appear to activate dimethylnitrosamine metabolically to a strong methylating agent, resulting in methylation of liver DNA at both the 7- and O6 positions of guanine.
>
> * * *
>
> Both rats and humans, then, appear capable of metabolically activating DMN to a strong methylating agent, which interacts with the same sites in liver DNA in both species.

Herron & Shank, *Methylated purines in human liver DNA after probable dimethylnitrosamine poisoning*, CANCER RESEARCH 40, 3116-3117 (1980), Ex. J. This conclusion is fully consistent with the conclusion in yet another article included on Dr. Catenacci's list, but not mentioned, referenced, or discussed, in his report.[4] That peer-reviewed publication from the World Health Organization, relied on by Plaintiffs' experts, states as follows:

> DNA adducts (in particular, O6-methylguanine) formed by the methyldiazonium ion generated during metabolism likely play a critical role in NDMA carcinogenicity. Observed variations in carcinogenicity among species and strains correlate well with

[4] Since Dr. Catenacci offered no opinions or analysis on the subject of the mechanistic evidence, the mere inclusion of articles addressing the subject on his list of materials considered—without being referenced, cited, or discussed in the actual report—cannot serve as a basis for him to provide opinions at trial. Fed. R. Civ. Proc. 26(a)(2)(B).

> variations in activity of O6-methylguanine DNA-methyltransferase. Putative pathways for the metabolism of NDMA are similar in rodents and humans, and indeed the formation of O6-methylguanine has been detected in human tissues exposed to NDMA.
>
> **Therefore, owing to the considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumour formation, and the apparent lack of qualitative species-specific differences in the metabolism of this substance, NDMA is highly likely to be carcinogenic to human**s.

Liteplo & Meek, *Concise International Chemical Assessment Document 38 – N-Nitrosodimethylamine*, at 23 (WHO 2002) emphasis added, Ex. K.

Dr. Catenacci simply ignored this entire category of data.

2. The Uneven Evaluation of Pottegård and Gomm.

Another area of weakness in Dr. Catenacci's methodology is his uneven treatment of the two valsartan-related human epidemiology studies he relied on, Pottegård and Gomm.[5] Pottegård was a cohort study performed using a Danish health claims database, and studying 5,150 subjects who took presumed contaminated and presumed uncontaminated valsartan. Dr. Catenacci relied heavily on Pottegård for his opinions, and in particular the conclusion in that study that there were no statistically significant associations to any cancer in general or any particular cancer. On the basis of the lack of a statistically significant association, he opined that the increased risk for colorectal cancer (1.46), and the increased risk of uterine cancer (1.81), were entitled to no consideration. As stated in his report: "No statistically significant associations were reported

[5] Pottegård, Kristensen, Ernst, Johansen, Quartarolo, & Hallas, *Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study*, B.M.J. 12, 362 (Sept. 2018), Ex. L; Gomm, Röthlein, Schüssel, Brückner, Schröder, Heß, Frötschl, Broich, & Haenisch, *N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer: A Longitudinal Cohort Study Based on German Health Insurance Data*, DEUTSCHES AERZTEBLATT INTERNATIONAL 118, 357-62 (2021), Ex. M.

between valsartan products potentially containing NDMA and any type of cancer…. [T]here was no individual cancer that had a statistically significant association of valsartan products potentially containing the NDMA impurity." (Catenacci 8/27/21 Report, at 38-39).

Yet, when discussing Gomm, a similar cohort study utilizing a German health claims database but with more than 770,000 patients who took potentially contaminated and uncontaminated valsartan, he denied then played down the finding in Gomm of a statistically significant increased risk for liver cancer. His report stated: "In other words, taking NDMA-containing the valsartan impurity was not associated with any increased risk in overall cancer or with any specific cancer. The analysis of individual cancer types, did show a slight statistically significant association, but not causation, between potentially NDMA-containing valsartan and liver cancer." (Catenacci 8/27/21 Report, at 39).[6] Dr. Catenacci played down and ascribed no true significance to the liver cancer finding in Gomm, ignored the fact that NDMA is metabolized in the liver, which he conceded, (9/14/2021 Daniel Catenacci Dep. Tr. 305:15-24), and ignored the conclusion by the authors that due to the short term nature of the study, "careful monitoring of potential further effects of NDMA-contaminated valsartan after longer periods is advisable." (Gomm, at 360). He also ignored his own publication stating that nitrosamines (which include NDMA and NDEA) are a risk factor for liver cancer, as set forth above. There is no question that Dr. Catenacci's methodology varied: lack of statistical significance was crucial to his embrace of the Pottegård findings, but when a statistically significant association with liver cancer was shown in Gomm, he ascribed no significance to that finding and strained to disregard it.

[6] Dr. Catenacci admitted in his deposition that the first sentence quoted above was inaccurate. (9/14/2021 Daniel Catenacci Dep. Tr. 305:9-14).

3. Dr. Catenacci's Concessions About the Weaknesses in Pottegård.

Dr. Catenacci acknowledged weaknesses in the Pottegård study design, including the small sample size, short term of the study, lack of information about the doses, and uncertainty as to whether the division of the patients into the presumed exposed and never exposed cohorts was correct, and acknowledged consequent serious questions as to the reliability of the data. (9/13/2021 Daniel Catenacci Dep. Tr. 233:10-18, 237:21-238:23, 239:21-240:10, 250:23-251:3, 253:4-13, 257:9-258:18, 262:3-273:24). Once confronted with the many problems with the study, he conceded that he needed more information to reach any definite conclusions about the significance of the data, undercutting any opinions relying on that data. (*Id.* at 273:23-24; 9/14/2021 Daniel Catenacci Dep. Tr. 294:6-295:18).

4. Unreliable Opinions Regarding Endogenous Formation of NDMA.

Another area of weakness was Dr. Catenacci's attempted reliance on the formation of NDMA due to biological processes inside the body to argue that the NDMA in the valsartan would have been insignificant. He opined that the levels of NDMA in the valsartan would be of no consequence as compared to the much higher levels that he opined would be formed in the body. However, when pressed, he admitted that there are multiple studies on this subject, applying a variety of mathematical models (NDMA is metabolized in the body, so it cannot be objectively measured in the body) with a variety of assumptions and conclusions as to the likely levels. And he ultimately admitted that he has **no opinion** as to what the levels of endogenous NDMA would be inside the body, and did not make any effort to calculate a level. (9/14/2021 Daniel Catenacci Dep. Tr. 354:211-356:7). If he has no opinion as to the level of endogenously formed NDMA in the body, he cannot say that the level is so high that other NDMA intake would be rendered insignificant.

5. Inadequate Understanding of Literature Regarding Monkey Studies.

Dr. Catenacci placed significant weight on a few studies on monkeys, positing that monkeys were not shown to develop cancer due to exposure to nitrosamines, and since they are closer to humans than rats, this is strong evidence against finding that there is general causation. (Catenacci 8/27/21 Report, at 44-45). However, when asked during his deposition if he also took into account monkey studies that did show development of cancer, he said he was not aware of any such study. (9/14/2021 Daniel Catenacci Dep. Tr. 371:12-21). The conclusions/findings of those other monkey studies demonstrate that this was important scientific data that he failed to consider. Specifically:

> Q. Let me -- Doctor, just to be clear, you're not aware of a study that utilized NDMA with monkeys and concluded that the data supported epidemiology implicating nitrosamines in causation of cancers of stomach and other organs?
>
> * * *
>
> Q. Yes or no? Did you see any such article, Doctor?
>
> A. I didn't see that in my research. I'm always happy to look at new data and analyze it if it comes available.

(9/14/2021 Daniel Catenacci Dep. Tr. 372:24-374:22; *see also* Anderson, Souliotis, Chhabra, Moskal, Harbaugh, and Kyrtopoulos, *N-nitrosodimethylamine-derived O(6)-methylguanine in DNA of monkey gastrointestinal and urogenital organs and enhancement by ethanol,* Int. J. Cancer 66, 130-4 (Mar. 1996) (stating: "Thus primate tissues, especially those of the gastrointestinal and urogenital organs. are sensitive targets for DNA adduct damage due to NDMA, and ethanol co-exposure leads to striking increases in adducts. **Our data support epidemiology implicating nitrosamines in causation of cancers of stomach and other organs, and alcohol as enhancing internal exposure to nitrosamines.**" (emphasis added)), Ex. N). The failure to be aware of, let

alone account for the data on both sides of this question is yet another significant methodological flaw.

THE *DAUBERT* STANDARD

The admissibility of expert testimony is determined pursuant to Federal Rule of Evidence 702. The party offering the proposed expert testimony bears the burden of establishing the admissibility of the testimony by a preponderance of the evidence. *Padillas v. Stork-Gamco, Inc.,* 186 F.3d 412, 417-18 (3d Cir. 1999). An "expert's opinions must be based on the methods and procedures of science, rather than on subjective belief or unsupported speculation." *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 742 (3d Cir. 1994) (citations and internal quotations omitted). Thus, "the expert must have 'good grounds' for his or her belief." *Id.* (quoting *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 590 (1993)). These good grounds must support each step of the analysis and, "*any* step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible." *Id.* at 745. Judges within this Circuit also consider how and when the methodology is used outside of litigation. *Paoli*, 35 F.3d at 742 (discussing reliability factors under *Daubert* and Third Circuit case law).

Furthermore, "*Daubert*'s gatekeeping requirement .... make[s] certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'" *Elcock v. Kmart Corp.*, 233 F.3d 734, 746 (3d Cir. 2000) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)); *see also Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F.Supp.2d 584, 594 (D.N.J.2002*)*, *aff'd,* 68 Fed. Appx. 356 (3d Cir. 2003). In addition, the following factors are relevant when determining reliability:

> (i) whether the expert's proposed testimony grows naturally and directly out of research the expert has conducted independent of the

> litigation (*see Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 43 F.3d 1311, 1317 (9th Cir. 1995)); (ii) whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion (*see General Elec. Co. v. Joiner,* 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)); (iii) whether the expert has adequately accounted for alternative explanations (*see Claar v. Burlington, N.R.R.,* 29 F.3d 499 (9th Cir. 1994)).

Magistrini, 180 F. Supp. 2d at 594–95.

I.
DR. CATENACCI'S OPINIONS SHOULD BE PRECLUDED PURSUANT TO *DAUBERT*

"**Both an expert's methodology and the application of that methodology must be reviewed for reliability**." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 792 (3d Cir. 2017), emphasis added. Directly relevant to this motion, "Flexible methodologies, such as the 'weight of the evidence,' can be implemented in multiple ways; despite the fact that the methodology is generally reliable, each application is distinct and should be analyzed for reliability." *Zoloft*, 858 F.3d at 795.

In granting a motion to preclude an expert under *Daubert*, this Court has observed:

> [C]ourts also need not admit mere conclusions or opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered…. Mere assumptions, without causal evidence or methodological analysis may be inadmissible.... Conclusions based only on the expert's experience, and testimony founded on methods that are not generally accepted or lack testable hypotheses may also fail to surmount the *Daubert* standard.

Player v. Motiva Enterprises LLC, No. Civ. 02–3216(RBK), 2006 WL 166452, at *6-7 (D.N.J. Jan. 20, 2006) (citations omitted) (Ex. O). In *Player*, this Court found the expert failed to satisfy the reliability requirement, as the expert failed to consider important facts without satisfactory explanation, among other things. *Id.* at *7. The Court held: "His method is untestable and

arbitrary, without a generally accepted, established, or peer reviewed methodology, and his evaluation was conducted without any real standards." *Id.* at *8.

Dr. Catenacci was barely aware of the NDMA/NDEA contamination of valsartan, if at all, until he was hired as a defense expert. (9/13/2021 Daniel Catenacci Dep. Tr. 11:6-11). This lack of knowledge and experience should result in greater scrutiny of the method actually applied by the expert. *See Elcock*, 233 F.3d at 747 (quoting *Paoli*, 35 F.3d at 742, n.8). Dr. Catenacci also formed his opinions in this case solely for the purposes of litigation. He has never performed research or thought about NDMA outside this litigation, with the exception of a single publication he authored and apparently forgot, which described nitrosamines as a known risk factor for biliary tract cancers**.** This should factor into the Court's determination of reliability:

> One very significant fact to be considered is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying. That an expert testifies for money does not necessarily cast doubt on the reliability of his testimony, as few experts appear in court merely as an eleemosynary gesture. But in determining whether proposed expert testimony amounts to good science, we may not ignore the fact that a scientist's normal workplace is the lab or the field, not the courtroom or the lawyer's office.

Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1317 (9th Cir. 1995). Expert testimony prepared solely for purposes of litigation, as opposed to testimony flowing naturally from an expert's scientific research or technical work should be viewed with some caution. *Magistrini*, 180 F. Supp. 2d at 594.

A. Dr. Catenacci's Methodology Was Fatally Flawed.

In order for Dr. Catenacci's opinions to be admissible, "the process or technique used in formulating the opinion [must be] ... reliable," and the principles and methods employed by the expert [must be] . . . applied reliably to the facts of the case. *Pineda v. Ford Motor Co.*, 520 F.3d

237, 247 (3d Cir. 2008) (citing *Paoli,* 35 F.3d at 742); *see also* Fed. R. Evid. 702, Advisory Committee's Note. Thus, "'an expert may not 'pick and choose' from the scientific landscape and present the Court with what he believes the final picture looks like.' **Where an expert ignores evidence that is highly relevant to his [or her] conclusion, contrary to his [or her] own stated methodology, exclusion of the expert's testimony is warranted.**" *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 242 (S.D.N.Y. 2018) (quoting *In re Rezulin Prods. Liab. Litig.*, 309 F.Supp.2d 531, 563 (S.D.N.Y. 2004)).

The failure by Dr. Catenacci to evaluate the mechanistic literature and evidence was surprising to say the least, and fatal to his methodology. This is a key piece of the puzzle, as demonstrated by the wealth of literature focused on the significance of this evidence—and including the compelling literature quoted above—which was on his list of materials considered but entirely ignored. Moreover, this literature was taken into account by the Plaintiffs' experts, as it is an important part of the foundation for the prevailing scientific consensus that NDMA and NDEA are probable human carcinogens.[7] Thus, the method that yielded the opinion in the report is unreliable. **"[I]f the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable**." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.,* 26

[7] The FDA has concluded that "NDMA and NDEA are probable human carcinogens and should not be present in drug products," the EPA considers NDMA and NDEA to be probable human carcinogens, and USP has said, "their presence in medicines, even at trace level is considered unacceptable because Nitrosamine impurities are probable human carcinogens." (FDA, *FDA presents interim limits of nitrosamines in currently marketed ARBs* (Dec. 19, 2018), https://tinyurl.com/4rkpdf5h, Ex. P; EPA, *N-Nitrosodimethylamine*, https://tinyurl.com/9krh69u9, Ex. Q; EPA, *N-Nitrosodiethylamine*, https://tinyurl.com/48y7nejw; USP, Summary, Highlights and Timeline of General Chapter <1469> Nitrosamine Impurities (July 20, 2018), Ex. R). [redacted] (SOLCO00024226, ZHP 129, Ex. S).

F. Supp. 3d 449, 460-61 (E.D. Pa. 2014) (emphasis added) (citing *In re Rezulin Prods. Liab. Litig.,* 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005)); *see also Zoloft*, 858 F.3d at 796 (stating, "all of the relevant evidence must be gathered, and the assessment or weighing of that evidence must not be arbitrary, but must itself be based on methods of science" (quoting *Magistrini*, 180 F. Supp. 2d at 602)). Therefore, the failure by Dr. Catenacci to "acknowledge or account for" the mechanistic studies, a key category of scientific literature relied on by Plaintiffs' experts strongly supporting the scientific consensus that NDMA and NDEA are probable human carcinogens, requires preclusion of his opinions.

Indeed, in order to ensure that the methodology is truly a methodology, rather than a mere conclusion-oriented selection process, there must be a scientific method that is used and explained. *Magistrini*, 180 F. Supp. 2d at 607. An expert's failure to comment on the potential weaknesses of the studies upon which an expert relies nor to acceptably explain why he did not accord more weight to other studies that did not align with his conclusions may render the opinion unreliable. *Magistrini*, 180 F. Supp. 2d at 584. Yet, that is exactly what Dr. Catenacci did.

In addition, as set forth above in detail, there are additional methodological flaws underlying the opinions here. These include Dr. Catenacci's heavy reliance on the Pottegård study based on the lack of statistical significance of the increased risks for colorectal and uterine cancer seen there,[8] **and result oriented dismissal of the Gomm study, despite the fact that the study found a statistically significant increased risk for liver cancer**. There is nothing even-handed

[8] Dr. Catenacci's hyper-focus on statistical significance is at odds with 3rd Circuit law. "**A causal connection may exist despite the lack of significant findings, due to issues such as random misclassification or insufficient power… A standard based on replication of statistically significant findings obscures the essential issue: a causal connection.** Given this, the requisite proof necessary to establish causation will vary greatly case by case." *Zoloft*, 858 F.3d at 794. Dr. Catenacci's approach was too rigid to comport with the applicable legal standard.

or objective about his weighing of the two studies, and this methodological inconsistency is also fatal to his ultimate opinion since he accords so much weight to the Pottegård study. *Zoloft*, 858 F.3d at 792 (affirming the trial court's exclusion of expert testimony that "failed to consistently apply the scientific methods … articulate[d], … deviated from or downplayed certain well-established principles of [the] field, and … inconsistently applied methods and standards to the data so as to support [an] a priori opinion," and concluding, "**By applying different techniques to subsets of the data and inconsistently discussing statistical significance, [an expert] does not reliably analyze the weight of the evidence**"). On top of that fatal flaw, when Dr. Catenacci was confronted with uncertainties arising from the Pottegård study design, including the inability to know to what extent the groupings of people who were or were not using contaminated valsartan were accurate, he conceded that he needed more information to reliably incorporate that study into his analysis. This eviscerated a key pillar of his opinion. *Id*.

Two other foundational elements of his opinion fell by the wayside during his deposition as well. First, since he conceded that he performed no calculations, and had no determination as to the level of endogenous nitrosamine formation, he cannot be permitted to assert that endogenous nitrosamine formation is so substantial that NDMA intake from valsartan is insignificant. Otherwise, he would be asserting a speculative concept, suggesting that the quantity must be very high—though he has no opinion to that effect. This would impermissibly leave the jury to guess or speculate along with him, which renders the opinion inadmissible. *Paoli*, 35 F.3d at 742 (stating, "*Daubert* explains that the language of Rule 702 requiring the expert to testify to scientific knowledge means that the expert's opinion must be based on the 'methods and procedures of science' rather than on 'subjective belief or unsupported speculation'; the expert must have 'good grounds' for his or her belief" (quoting *Daubert*, 509 U.S. at 590)); *Player*, 2006 WL 166452, at

*7.

Finally, he relied heavily on two studies involving a combined total of thirteen monkeys who were reported not to show an increased risk for cancer due to NDMA intake, in an effort to assert that the animal studies do not prove anything about the impact on humans. However, when confronted with countervailing literature showing that monkeys have been shown to develop cancer due to NDMA, he conceded he was not aware of and had not taken into account that literature. This is yet another glaring methodological flaw pulling out yet another pillar supporting his opinion. *Zoloft*, 858 F.3d at 796; *Mirena II*, 341 F. Supp. 3d at 242 (quoting *Rezulin*, 309 F. Supp. 2d at 563).

The combination of so many methodological flaws is enough to preclude Dr. Catenacci's opinions. When considered against the backdrop of an overwhelming scientific consensus that NDMA and NDEA are human carcinogens, the gaps in the analysis are all the more significant. As a result, Dr. Catenacci's methodology is irreparably flawed, and his opinions are inadmissible.

CONCLUSION

For the foregoing reasons, Dr. Catenacci should be precluded from offering his opinions related to general causation.

Respectfully,

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